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Outcome of Alcohol Septal Ablation in Mildly Symptomatic Patients With Hypertrophic Obstructive Cardiomyopathy: A Long-Term Follow-Up Study Based on the Euro-Alcohol Septal Ablation Registry

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Background—The long-term efficacy and safety of alcohol septal ablation (ASA) in patients with highly symptomatic hypertrophic obstructive cardiomyopathy has been demonstrated. The aim of this study was to evaluate the long-term outcomes of mildly symptomatic patients with hypertrophic obstructive cardiomyopathy treated with ASA.

Methods and Results—We retrospectively evaluated consecutive patients enrolled in the Euro-ASA registry (1427 patients) and identified 161 patients (53 ± 13 years; 27% women) who were mildly symptomatic (New York Heart Association [NYHA] class II) pre-ASA. The median (interquartile range) follow-up was 4.8 (1.7–8.5) years. The clinical outcome was assessed and compared with the age- and sex-matched general population. The 30-day mortality after ASA was 0.6% and the annual all-cause mortality rate was 1.7%, which was similar to the age- and sex-matched general population ($P=0.62$). A total of 141 (88%) patients had resting left ventricular outflow tract gradient at the last clinical checkup ≤ 30 mm Hg. Obstruction was reduced from 63 ± 32 to 15 ± 19 mm Hg ($P<0.01$), and the mean NYHA class decreased from 2.0 ± 0 to 1.3 ± 0.1 ($P<0.01$); 69%, 29%, and 2% of patients were in NYHA class I, II, and III at the last clinical checkup, respectively.

Conclusions—Mildly symptomatic hypertrophic obstructive cardiomyopathy patients treated with ASA had sustained symptomatic and hemodynamic relief with a low risk of developing severe heart failure. Their survival is comparable to the general population. (*J Am Heart Assoc.* 2017;6:e005735. DOI: 10.1161/JAHA.117.005735.)

Key Words: ablation • hypertrophic cardiomyopathy • outcome

The prognosis in patients with hypertrophic obstructive cardiomyopathy (HOCM) who self-report mild or no symptoms is significantly worse than that of the age- and sex-matched general US population.¹ Furthermore, even in the absence of cardiac symptoms, severity of the left ventricular

(LV) outflow tract obstruction (LVOTO) is independently associated with a higher risk of adverse clinical outcome.^{1–5}

Based on current guidelines, alcohol septal ablation (ASA) may only be performed in highly symptomatic HOCM patients in NYHA class III or IV and in those with recurrent exertional

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syncope associated with a LVOTO ≥ 50 mm Hg.^{6,7} In these patients, ASA has been shown to be very effective in reducing LVOTO and associated symptoms.^{8–19} However, data on the outcomes of ASA in mildly symptomatic patients are scarce. We examined the long-term outcomes of ASA in patients, who self-report dyspnea of functional class New York Heart Association (NYHA) II and were included in the Euro-ASA registry.

Methods

Patients

A total of 1427 consecutive patients (49% women, 58.1 ± 13.6 years) treated with ASA for HOCM in 11 European centers were enrolled in the Euro-ASA registry.

We identified 161 patients (11%; 27% women) with baseline NYHA class II dyspnea and LVOTO ≥ 50 mm Hg at rest or after provocation, who were included in this study. None reported angina or syncope. Patients were treated with ASA between January 1996 and May 2016. Some of the patients have been included in previous reports.⁴ Informed consent was given by each patient, and the study was performed in agreement with The Declaration of Helsinki.

Alcohol septal ablation was performed in mildly symptomatic patients who were diagnosed with HOCM that was refractory to medical therapy. Because ASA in mildly symptomatic patients is not generally recommended, the procedure was only performed in patients who had significantly reduced quality of life attributed to dyspnea and had a strong wish for symptomatic improvement. All patients were carefully informed about institutional experience with septal reduction therapy techniques and accepted the risk of the procedure.

Interventional Procedure and Follow-up

Details of the ASA technique used in the Euro-ASA registry were published previously.⁴ Most patients had routine clinical examination 3 to 6 months post-ASA and subsequently once every year. The follow-up program included recording of events, symptoms, physical examination, ECG, and echocardiographic examination, including risk stratification for sudden cardiac death (SCD). In patients with an implanted pacemaker or defibrillator (ICD), the device's memory and function were assessed, and ICD therapy was recorded. All clinical adverse events were confirmed by reviewing the medical records and respective national registries of deaths. For patients who died outside the participating hospitals, interviews and/or mail communications with the next of kin and/or the treating family doctor were performed to determine the cause of death.

Definitions and Study End Points

Clinical outcome post-ASA was assessed and all-cause mortality registered. Sudden death was defined as instantaneous and unexpected natural death within 1 hour after witnessing collapse in a previously stable patient or death during sleep. An appropriate ICD discharge was defined as the first post-ASA device intervention triggered by ventricular tachycardia or fibrillation. A death that could not be clearly attributed to any cause was classified as death of unknown cause.

In this study dealing with mildly symptomatic patients, we wanted to determine (1) survival post-ASA, as compared to the sex- and age-matched general population; (2) symptomatic improvement post-ASA; (3) progression of heart failure symptoms post-ASA; and (4) predictors of adverse clinical outcome.

Statistical Analysis

All data were edited and analyzed by 2 independent statisticians (M.M. and E.H.). Student *t* tests, chi-square tests, and Kaplan–Meier survival analysis were used, when appropriate. Expected survival was calculated from age- and sex-specific mortality rates obtained from the Human Mortality Database (University of California, Berkeley, CA and Max Planck Institute for Demographic Research, Rostock, Germany; available at www.mortality.org or www.humanmortality.de). Mortality rates were calculated for each individual and combined to form an expected summary curve for the internationally mixed general population. Expected and observed mortalities were compared by using the 1-sample log-rank test, which provided a standardized mortality ratio and the 95% CI. Cox proportional hazards regression was used to identify predictors of all-cause death and all-cause death or appropriate ICD discharge or resuscitation. The prognostic effects of the following parameters were evaluated, first in a univariate model: age at time of ASA; sex; absence of functional improvement post-ASA; baseline and residual dyspnea; LVOTO, and septal thickness. Second, variables with a $P < 0.15$ were entered into a multivariable analysis, which was performed using a backward step-wise multiple Cox's regression. A probability less than 0.05 was considered to indicate a statistically significant result. All reported *P* values were 2-sided. The statistical software GraphPad (release 6.05; GraphPad Software Inc, La Jolla, CA) and Stata (release 9.2; StataCorp LP, College Station, TX) were used.

Results

Short-Term Outcome

A total of 161 consecutive, mildly symptomatic HOCM patients (27% women) underwent ASA. Baseline clinical and

echocardiographic characteristics of the patient cohort are summarized in Table 1. All procedures were performed with myocardial contrast echocardiography guidance. Volume of injected alcohol during ASA was 2.0 ± 1.1 mL.

One patient (0.6%) died of ventricular fibrillation 2 days post-ASA. Intra- or periprocedural sustained ventricular tachycardia/VF requiring electrical cardioversion occurred in 4 (2.5%) additional patients. The 30-day mortality rate was 0.6%.

Of 149 patients without an implanted pacemaker or ICD pre-ASA, intra- or periprocedural complete heart block was identified in 27 (18%), and 14 (9.4%) had a pacemaker implanted before hospital discharge.

Long-Term Outcomes

None of the 160 (99%) patients who survived the first month post-ASA were lost to follow-up (median follow-up, 4.8 [interquartile range {IQR}, 1.7–8.5; maximum, 16.2] years). Clinical and echocardiographic data regarding outcomes >30 days post-ASA are summarized in Table 1.

At last clinical checkup, the resting left ventricular outflow tract (LVOT) gradient was reduced from 63 ± 32 to 15 ± 19 mm Hg, which translates to a mean LVOTO reduction of 77%. In 141 (88%) patients, the LVOTO was ≤ 30 mm Hg at the last clinical checkup. A total of 111 (69%) patients were in NYHA class I, 46 (29%) were in NYHA class II, and 3 (2%) were in NYHA class III at the last clinical checkup.

Fifteen (9.3%) patients underwent repeated septal reduction therapy attributed to insufficient symptomatic relief; 13 (8.1%) underwent repeated ASA, 3 (1.9%) underwent myectomy, and 1 (0.7%) underwent myectomy after re-ASA. During

Table 1. Clinical and Echocardiographic Characteristics at Baseline and Follow-up of Mildly Symptomatic Patients With HOCM Treated With ASA (Mean \pm SD)

	Baseline (n=161)	Follow-up >30 Days (n=160)	P Values
Age, y	53.4 \pm 12.9	58.9 \pm 12.6	
Dyspnea, NYHA class	2.0 \pm 0	1.3 \pm 0.5	<0.01
Episodes of syncope, %	0	5 (3.1)	<0.03
LV gradient at rest, mm Hg	63.3 \pm 31.7	14.6 \pm 19.0	<0.01
LV diameter, mm	43.8 \pm 6.7	46 \pm 5.8	<0.01
Left atrium diameter, mm	47.1 \pm 6.9	44.7 \pm 6.4	<0.01
LV ejection fraction, %	71 \pm 9	68 \pm 8	0.02
Basal septum thickness, mm	20.6 \pm 4.3	15.7 \pm 4.4	<0.01

ASA indicates alcohol septal ablation; HOCM, hypertrophic obstructive cardiomyopathy; LV, left ventricular; NYHA, New York Heart Association.

Table 2. Causes of Death After ASA

Sudden death	33%
Noncardiovascular death	33%
Cardiovascular death	20%
Unknown cause	13%

ASA indicates alcohol septal ablation.

the study period, 9 patients (5.6%) had an ICD implanted; 1 for secondary prevention and 8 for primary prevention according to current guidelines. Overall, of 18 (11.3%) patients with an ICD (median age at ASA, 50.0 ± 11.7 years; 28% women; median [IQR] follow-up, 3.0 [1.7–8.9] years), 4 (22%) experienced an appropriate ICD discharge (4.5% per year).

A total of 15 (9.3%) deaths occurred during 895 patient-years of follow-up, which translates to a rate of 1.7 deaths per 100 patient-years. Five of these patients died suddenly, which converts to a rate of 0.6 sudden deaths per 100 patient-years. In these patients, ASA was performed at an average age of 61.6 ± 11.1 years and the mean survival was 5.2 ± 4.2 years post-ASA. Causes of death are summarized in Table 2.

Survival free of all-cause mortality at 1, 5, and 10 years was 97% (95% CI, 93–99), 94% (95% CI, 89–97), and 87% (95% CI, 78–93), respectively. This survival was comparable to the expected survival in an age- and sex-matched general population ($P=0.62$; Figure 1). According to multivariable analysis, the independent predictors of all-cause mortality were age at ASA (hazard ratio [HR], 1.05; 95% CI, 1.00–1.10; $P=0.04$) and absence of improvement in NYHA class score at the last clinical check-up (HR, 3.77; 95% CI, 1.09–13.11; $P=0.04$).

Survival free of all-cause mortality combined with the first appropriate ICD discharge or resuscitation at 1, 5, and

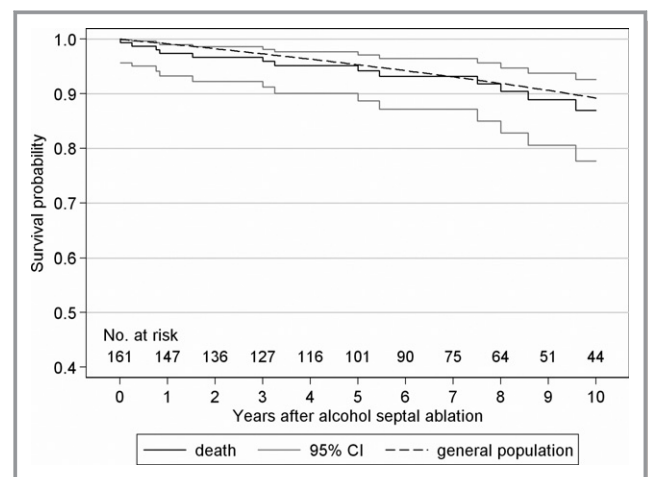


Figure 1. Kaplan-Meier survival curves describing all-cause mortality, including 95% CI and compared to that expected in the general population after adjustment for age and sex ($P=0.62$).

10 years was 97% (95% CI, 93–99), 91% (95% CI, 84–94), and 87% (95% CI, 80–93), respectively. This observed survival free of (aborted) death was comparable to the expected survival for the age- and sex-matched general population ($P=0.33$; Figure 2). Multivariable analysis performed to identify the predictors of all-cause mortality including appropriate ICD discharge and resuscitation found the only independent predictor to be the absence of NYHA class improvement (HR, 3.30; 95% CI, 1.14–9.54; $P=0.03$).

Discussion

Alcohol septal ablation for the HOCM was introduced more than 2 decades ago,⁸ and its early use was restricted to highly symptomatic patients. It has repeatedly been demonstrated that these patients benefitted symptomatically.^{4,5,8–19} Some studies also suggested a positive prognostic influence of septal reduction therapy (ASA or surgical myectomy), especially if post-treatment LVOTO was markedly reduced.^{5,9,20} The careful therapeutic strategy, focused on the highly symptomatic and highest risk patients, was mirrored by both American and European guidelines on hypertrophic cardiomyopathy (HCM).^{6,7} However, recent data have suggested a significant impact of LVOTO on long-term outcome in patients with HOCM, independent of symptoms.^{1–3,5,9} This led us to analyze post-ASA outcomes of patients treated for mild symptoms and severe LVOTO. The essential findings of this study are as follows: (1) Carefully selected patients with mild symptoms (NYHA class II) and severe LVOTO treated with ASA had a long-term prognosis similar to that of the sex- and age-matched general population; (2) these patients were at

minimal risk (2%) for developing severe heart failure (NYHA class >II) symptoms during long-term (median 4.8 years) follow-up; (3) 70% of patients achieved NYHA functional class I; (4) resting LVOTO assessed by continuous wave Doppler echocardiography was reduced by 77% at the last clinical checkup, and 88% of patients had LVOT gradient ≤ 30 mm Hg at the last clinical check-up; and (5) the absence of NYHA class improvement was independently associated with higher long-term mortality.

There remains a significant knowledge gap in the therapeutic strategy for asymptomatic or mildly symptomatic patients with severe LVOTO. Not surprisingly, the current therapeutic approach with septal reduction therapy (ASA or myectomy) is based on evidence obtained exclusively from highly symptomatic patients; a multicenter North American registry ($n=874$; 55 ± 16 years; rest gradient, 70 ± 38 mm Hg; 78% in NYHA class III/IV) demonstrated a 5-year survival rate of 86%,²¹ and previously reported European experience ($n=1275$; 58 ± 14 years; rest gradient, 67 ± 36 mm Hg; NYHA class 2.9 ± 0.5) showed a 5-year survival rate of 89%.⁴ A 5-year survival rate reported in this study is 94%. This difference was expectable, given that NYHA class pre-ASA was recently identified as an independent predictor of all-cause mortality (HR, 1.5).⁴

However, scarce data and experience from clinical practice suggest that severe LVOTO may be harmful irrespective of the severity of symptoms.^{1–3,5} This notion was supported by a study ($n=544$; 59 ± 16 years) from the Mayo Clinic reporting on the long-term outcome of patients with HOCM who were free of severe symptoms at baseline.¹ Patients with LVOT gradient >64 mm Hg at baseline had a 10-year survival of only 53%, and severe LVOTO was an independent predictor of adverse clinical outcome. Furthermore, death or severe symptoms occurred in 68% of these patients within 10 years after the first evaluation.¹ This finding is important, especially in the light of recent studies showing a $\leq 1\%$ ASA-related mortality, with an enduring effect on LVOTO and associated symptoms following the procedure.^{4,13,22} Thus, on one hand, LVOTO is considered a risk factor of long-term outcome in HOCM patients irrespective of their symptoms, and on the other hand, ASA performed in dedicated centers seems to be safe and effective in diminishing LVOTO.^{1–5,8–19,22} The results of the present study should be weighed against this background, and although our study has limitations as discussed below, the results clearly challenge the established clinical standard of treating only highly symptomatic HOCM patients with ASA.

The fact that current treatment guidelines on HCM generally recommend watchful waiting until development of severe symptoms before invasive treatment parallels established practice in patients with severe aortic stenosis.^{6,7} However, a growing body of evidence suggests that long-term

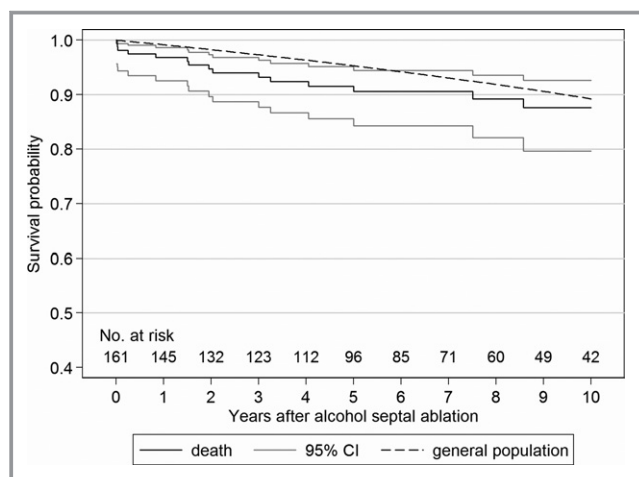


Figure 2. Kaplan–Meier survival curves describing all-cause mortality plus the first appropriate ICD discharge or resuscitation, including 95% CIs, and compared to survival expected in the general population after adjustment for age and sex ($P=0.33$). ICD indicates implanted defibrillator.

outcome in asymptomatic patients with severe aortic stenosis managed conservatively is dismal, and that earlier invasive treatment could lead to improved outcomes.^{23–25} Along this line, it appears possible that mildly symptomatic HOCM patients with severe LVOTO could benefit from early invasive treatment aimed at LVOTO reduction. However, decision making for early septal reduction therapy in mildly symptomatic patients with HOCM is complex, and these patients may represent a diverse group. Furthermore, septal reduction therapy (myectomy or ASA) should only be performed in dedicated centers that can achieve a procedure-related mortality rate less than 1%.²⁶

Notably, the European Society of cardiology HCM risk calculator used to estimate the risk for SCD considers some mildly symptomatic patients with LVOTO to be eligible for ICD implantation.²⁷ Although patients after septal reduction therapy should not be subject to SCD risk evaluation with this calculator, one can speculate that diminishing LVOTO by invasive treatment could lower the risk of SCD in some of these patients.¹⁶ This may not only improve survival, but might also reduce the need for ICD implantation. Such a clinical scenario is not uncommon, but an adequate therapeutic strategy has not yet been determined in these patients.^{6,7} Randomized trials would be ultimately required to determine whether the primary therapeutic goal in such patients should be invasive reduction of LVOTO and/or ICD implantation, but, in the meantime, more retrospective data, such as those presented in the current study, are needed on outcomes in mildly symptomatic HOCM patients, especially those with severe LVOTO.

This study has several limitations. First, it was a retrospective analysis of prospectively collected data in several European countries, which is associated with certain inherent limitations. The centers participating in the Euro-ASA Registry may differ in patient selection, ASA technique, and post-ASA evaluation. Nevertheless, some principal tenets were used in all centers; all ASA procedures were guided by myocardial contrast echocardiography, and post-ASA assessments included clinical evaluation, echocardiographic examination, and device interrogation in all centers. Second, based on recent real-world data from the US Nationwide Inpatient Database demonstrating marked differences in ASA safety between low- and high-volume centers,²² caution is needed before generalizing the current results, because these patients were treated in experienced catheterization centers and subsequently followed in dedicated HCM clinics. Moreover, all patients were carefully selected for ASA, including presence of septal and mitral apparatus anatomy appropriate for the procedure. Third, although the Euro-ASA registry is the largest reported ASA cohort so far, it still included a relatively small number of mildly symptomatic patients for ultimate analysis of their clinical outcome. Nevertheless, the present

results are consistent with previously published evidence and suggest favorable clinical outcome of these patients. Fourth, this study is based on self-reported level of symptoms. However, some patients tend to adapt themselves to their limitation and therefore admit a lower degree of symptom severity, which might affect baseline characteristics of this cohort.

Conclusions

Carefully selected, mildly symptomatic HOCM patients with severe LVOTO treated with ASA in dedicated centers have long-term prognosis comparable to that of the age- and sex-matched general population. These patients are at minimal risk for developing severe heart failure and most of them achieve long-term functional class NYHA I and LVOT gradient ≤ 30 mm Hg.

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Disclosures

None.

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